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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,634	04/01/2004	Tania Kastelic	608352000100	8704
25226 7590 11/26/2008 MORRISON & FOERSTER LLP 755 PAGE MILL RD PALO ALTO, CA 94304-1018			EXAMINER QIAN, CELINE X	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/814,634

Applicant(s)

KASTELIC ET AL.

Examiner

CELINE X. QIAN

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9,10,13-15,24-36 and 38-49 is/are pending in the application.
- 4a) Of the above claim(s) 10,13 and 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9,15,24-36 and 38-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 9, 10, 13-15, 24-36, 38-49 are pending in the application. Claims 10, 13 and 14 are withdrawn from consideration for being directed to non-elected subject matter. Claims 9, 15, 24-36 and 38-49 are currently under examination.

Response to Amendment

The rejection of claims 9, 15, 23-29 under 35 U.S.C.112 1st paragraph has been withdrawn in light of Applicant's amendment.

The rejection of claims 30-39 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicant's amendment.

The rejection of claims 9, 24-27, 29-34, 36-39 under 35 U.S.C.102 (b) has been withdrawn in light of Applicants' amendment.

Claims 9, 15, 24-36, 38-49 are rejected under 35 U.S.C.103 (a) for reason discussed below, necessitated by Applicant's amendment.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 15, 24-27, 29-34, 36, 38-41 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banholzer et al.

Zubiaga et al. disclose an expression vector comprising *c-fos* promoter operatively linked to globin gene, wherein several ARE isolated from *c-fos* is inserted into 3'UTR of the globin gene, pBBB+ARE, resulting in sets of cell lines comprises different expression constructs. Zubiaga et al. also disclose a control plasmid p Δ ARE, in which it comprises the 53bp 3' UTR from *c-fos* inserted downstream of β -globin stop codon (see page 2220, 2nd col., Result section, 1st paragraph). Zubiaga et al. also disclose that a plasmid pRSV-lacZ, comprising a gene coding for expression of lacZ, 5' and 3'UTR for expression of said gene without mRNA instability sequence (see page 2221, 1st col., 2nd paragraph, lines 4-9), which serves as an internal control for correction for variations in transfection efficiency. Zubiaga et al. further disclose a second control plasmid pGB-ARE contains a fragment from GAPDH coding sequence inserted in frame within the 5' half of the globin coding region, and same elements from pBBB+ARE (see page 2221, bridging paragraph). Lastly, Zubiaga et al. disclose that the internal control construct, the second control plasmid pGB-ARE and the expression plasmid pBBB+ARE are co-transfected into NIH-3T3 cells (see page 2221, 1st col., 2nd paragraph, lines 1-4), and plasmid constructs comprising different ARE sequence are transfected separately into NIH-3T3 cells (see for example, Figure 1). Zubiaga et al. do not teach an assay system for screening compounds which

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destabilize mRNA that comprises a cell line as claimed in claim 9 and a test compound, and wherein the cell line is stably transfected.

Banholzer et al. disclose that rapamycin promotes degradation of IL-3 transcripts at posttranscriptional level via 3' UTR (see page 3257, 2nd col., 1st paragraph). Banholzer et al. disclose two cell lines stably transfected with IL-3 expression system either with (VD1-M1) or without (VD1-M1 Δ AU) mRNA instability sequence (3' UTR) (see page 3256, 1st col., lines 1-3). Banholzer et al. teach that the cell lines V2D1, V3D6 are autocrine tumor cell lines, as such the cell lines are of native cell type in which the IL3 RNA instability sequence is produced (see page 3255, 2nd col., Result section: 1st paragraph). Banholzer et al. also disclose that following rapamycin and FK506 treatment, endogenous and exogenous wild type IL-3 decayed with very similar kinetics (see Figure 3b, left panel) whereas the exogenous mutant IL-3 mRNA level is not affected by either compound (Figure 3b, right panel, and 3c). The method and assay system disclosed by Banholzer et al. identifies rapamycin and FK506 as compounds that induce mRNA degradation.

It would have been obvious for one of ordinary skill in the art to develop an assay system as taught by Banholzer that is able to screen compounds such as rapalogs for their ability to modulating the mRNA instability sequence. Based on the teaching of Zubiaga, the ordinary skilled in the art would have been motivated to screening compounds that would affect ARE sequence instability using the heterologous expression construct as disclosed in Zubiaga et al. One of ordinary skill in the art would also be motivated to use stably transfected cell lines because they are easy to maintain such that one does not have to do transfection every time to test a compound. The level of skill in the art is high. Absent evidence from the contrary, one of

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ordinary skilled in the art would have reasonable expectation of success to use the cell line taught by Zubiaga as a system to test compounds and make the cell line a stably transfected cell for said purpose. Therefore, the claimed invention would have been *prima facie* obvious at the time the invention was made.

Claims 28 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Lemm and Ross (Molecular and Cellular Biology, 2002, Vol 22, No.12, pages 3959-3969).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach a coding region instability determinant as the instability sequence.

Lemm and Ross teach a 249 nucleotide coding region from c-myc destabilizes c-myc mRNA. Lemm and Ross also teach that said nucleotide sequence destabilizes beta-globin mRNA when inserted in frame within the coding region of said beta-globin gene (see page 3959, 2nd col., 2nd paragraph).

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect coding region instability determinants (CRD) from c-myc based on the combined teaching of Zubiaga, Banzholer and Lemm and Ross. The ordinary artisan would insert the CRD into the expression construct as

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taught by either Zubiaga or Banzholer and determine whether such instability is modulate by any compound such as the Rapamycin destabilizes IL-3 mRNA. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the CRD into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As for the priority date for claims 28 and 35, it does not enjoy the priority to the 09/869,159 application because the limitation of "DNA corresponding to one or more CRD from the coding region of said naturally occurring genes" is not described in the '159 application. The instant application is a CIP of the '159 application, and the newly presented material in the instant application has priority date of the instant application, which is 4/1/04. Therefore, the Lemm and Ross references published in 2002 is considered as prior art for this reason.

Claim 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Kastelic et al (Cytokine, 1996. Vol. 8, No. 10, pages 751-761).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the instability sequence is from the gene coding for IL-1 β .

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Kastelic et al. teach IL-1 β , IL-6 and TNF- α mRNA comprises instability sequence AUUUA, in the 3' UTR (see page 757, Table 1). Kastelic et al. further teach that said AU elements are sufficient to confer the destabilizing effect of radicicol analogue A in an reporter gene expression system (see page 758, 1st col., 2nd paragraph).

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect the AUUUA mRNA instability sequence from IL-1 β and TNF- α based on the combined teaching of Zubiaga, Banzholer and Kastelic et al. The ordinary artisan would insert the AUUUA instability sequence from IL-1 β and TNF- α into the expression construct as taught by either Zubiaga or Banzholer and determine whether such instability is modulate by any compound other than radicicol analogue A. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the AUUUA instability sequence from IL-1 β and TNF- α into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Levy et al (JBC, 1996, Vol. 271, No. 5, pages 2746-2753).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the instability sequence is from the gene coding for VEGF.

Levy et al. teach 3'UTR from the VEGF coding sequence comprises AU rich sequences that may be responsible for the increased expression of VEGF in response to hypoxia (see page 2749, 2nd col., 4th paragraph), wherein deletion of the sequences increases the mRNA stability (see page 2748, 1st col., last paragraph).

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect the AUUUA mRNA instability sequence from VEGF based on the combined teaching of Zubiaga, Banzholer and Levy et al. The ordinary artisan would insert the AUUUA instability sequence from VEGF into the expression construct as taught by either Zubiaga or Banzholer and determine whether such instability is modulate by test compounds similar to the effect of hypoxia. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention

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was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the AUUUA instability sequence from VEGF into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Rajagopalan et al (Journal of Neurochem. 2000. Vol74, pages 52-59).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the instability sequence is from the gene coding for APP.

Ragagopalan et al. teach that a 29 nt nucleotide in the 3'UTR of the APP gene confers instability of the APP mRNA, wherein its function may be inhibited by a combination of growth factors (see abstract, and page 55, 2nd col., through page 56, 1st col. and Figure 3).

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect the 29nt mRNA instability sequence from APP based on the combined teaching of Zubiaga, Banzholer and Rajagopalan et al. The ordinary artisan would insert the 29nt instability sequence from APP into the expression construct as taught by either Zubiaga or Banzholer and determine whether such instability is

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modulate by test compounds similar to the effect of growth factors. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the 29nt instability sequence from APP into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The priority date for claim 44 is determined as 4/1/04, which is the filing date of the instant application. This claim does not enjoy the priority to the 09/869,159 application because the limitation of "mRNA instability sequence from APP gene" is not described in the '159 application. The instant application is a CIP of the '159 application, and the newly presented material in the instant application has priority date of the instant application, which is 4/1/04. Therefore, the Rajagopalan reference published in 2000 qualifies as prior art.

Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Capaccioli et al. (Oncogene, 1996, Vol.13, pages 106-115).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the instability sequence is from the gene coding for bcl-2 α .

Capaccioli et al. teach that bcl-2/Ig H expression is up-regulated in t(14,18) cells by treating cells with antisenses to the hybrid gene. Capaccioli et al. also teach that there is an AU

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rich region at the 5' end of the 3' UTR of the bcl-2/IgH gene which might be masked by the antisense, such that the expression is increased. Capaccioli et al. teach that this AU motif is repeated in this region and highly conserved in mouse, chicken and human bcl-2 genes (see page 112, 2nd col.)

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect the AU rich motif mRNA instability sequence from bcl-2 based on the combined teaching of Zubiaga, Banzholer and Capaccioli et al. The ordinary artisan would insert the AU rich instability sequence from bcl-2 gene into the expression construct as taught by either Zubiaga or Banzholer and determine whether such instability is modulate by test compounds or other factors that would regulate post transcriptional bcl-2 gene expression. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the AU rich instability sequence from bcl-2 into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Yeilding et al (Molecular and Cellular Biology, 1996.Vol. 16, No. 7, pages 3511-3522).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the instability sequence is from the gene coding for VEGF.

Yeilding et al. teach that the 3'UTR and exon 3 of the c-myc gene coding sequence comprises sequences that are responsible for maintaining low level of mRNA during myoblast differentiation (see page bridging paragraph from page 3513-3514), wherein deletion of the sequences increases the mRNA stability (see page 3517, 1st col-2nd col., and bridging paragraph of page 3518-3519).

The obviousness of making a stably transfected cell line comprising constructs coding for a protein with instability sequences and use said cell line to identify compound that affect stability of the sequences were discussed above. It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by Zubiaga et al. and/or Banzholer to test compounds that affect the mRNA instability sequence from c-myc based on the combined teaching of Zubiaga, Banzholer and Yielding et al. The ordinary artisan would insert the 3'UTR or the exon 3 instability sequence from c-myc into the expression construct as taught by either Zubiaga or Banzholer and determine whether such instability is modulate by test compounds similar that regulates c-myc expression. All the claimed elements were known in prior art and one skilled in the art could have combined the

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elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the instability sequences from c-myc into a construct which can then be stably transfected into a cell line for testing compounds. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Banzohler et al., as applied to claims 9, 15, 24-27, 29-34, 36, 38, 39, 41 and 49, and further in view of Zhang et al (Biochemical and Biophysical Research Communications, 1996. Vol. 227, No.3, pages 707-711).

The teachings of Zubiaga and Banzholer et al. are discussed above. However, Zubiaga and Banzholer et al. references do not teach the detectable signal is detected directly.

Zhang et al. teach several reporter genes, such as secreted alkaline phosphatase, B-gal, firefly luciferase, CAT and GFP can be used in *in vivo* reporter assays (see page 707, 3rd paragraph). Zhang et al. further teach that GFP is an important reporter because it has advantages over other reporter for not requiring additional cofactors, substrates, or additional gene products. Zhang et al. further teach the generation of a humanized EGFP that has great sensitivity and stability (see bridging paragraph of 708 and 709).

It would have been obvious to one of ordinary skill in the art to develop a method of screening compound that modulate mRNA instability by using an expression cassette comprising a reporter in which the signal may be directly measured such as GFP reporter gene and a mRNA

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instability sequence inserted into 3'UTR of said reporter gene based on the teaching of Banhozler et al., Zubiaga et al., and Zhang et al. Banhozler et al. has demonstrated that compounds such as rapamycin can be tested for its ability to affect mRNA instability in a construct comprising the mRNA sequence down stream of the AP gene. Since the ARE instability region has already been identified as taught in Zubiaga et al., it can be inserted to 3'UTR of any known gene, including a reporter gene such as GFP. One of ordinary skill in the art would have been motivated to do so because the advantages offered by a GFP reporter over measuring mRNA stability by Northern blot, such as the non-invasive nature of direct measurement of fluorescent intensity. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make a stably transfected cell line comprising an expression cassette comprising a GFP reporter and mRNA instability sequence to screen for compounds that modulate mRNA instability. All the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention was made. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Conclusion

No claims are allowed.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636